**RESPONSE**

Claims 1-46 of the subject application are pending, claims 1-5, 13-15, 20-22, 26-28, and 33-40 have been withdrawn subject to a restriction requirement, claims 16 and 29 have been cancelled, and claims 6-12, 16-19, 23-25 and 29-32 were rejected. Applicants have added new claim 47 and gave cancelled claims 41-44. Accordingly, claims 45-47 are presently being examined.

In view of the following Amendment and Response, applicants respectfully request that the Examiner pass the above-identified application to issue.

**Support for the Amendments**

Applicants have added new claim 47 and gave cancelled claims 41-44 in order to more clearly describe and distinctly claim the subject matter of applicants' method for screening candidate compounds capable of inhibiting HMGI biological activity. Specifically, applicants have added claim 47 which combines old claims 41 and 44 in order to overcome the Examiner's 35 U.S.C. Section 112, second paragraph, as being incomplete for omitting essential steps.

These amendments to the claims are fully supported in the specification as originally filed, and thus no new matter is introduced by these amendments in accord with 35 U.S.C. Section 132. Accordingly, applicants request entry of these amendments.

**Rejection of Claims 41-46 under 35 U.S.C. Section 112, Second Paragraph.**

The Examiner has rejected claims 41-46 under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that claims 41-46 refer to an inhibition of HMGI biological activity, however, the specification does not clearly define biological activity of HMGI proteins. Without a clear definition, the Examiner contends that it is not possible to understand the metes and bounds of the patent protection desired. Applicants traverse the Examiner's rejection.

In summary, the function of the HMGI proteins is to regulate the expression of other genes. Applicants have set out the definition of biological activity of HMGI proteins in the specification at, for example, page 53, lines 20-27.

> As architectural components of the enhanceosome, a higher order transcription enhancer complex that forms when several distinct transcription factors assemble on DNA in a stereospecific manner, HMGI proteins function to regulate the expression of downstream target genes. Disruption of the enhanceosome assembly, by interfering either with protein-DNA or protein-protein interactions of HMGI proteins results in loss of transcriptional regulation. Small molecule drugs which interfere with the function of HMGI proteins as architectural factors can therefore be used to regulate growth and development of adipose tissue.

The language of claim 15 which requires that the bottom camber surface is located below and extends generally parallel with respect to said chord line is neither vague nor indefinite, in our view. It is clear from this language

precisely what the appellant intends his claim language to cover: an airfoil body having a bottom surface below and parallel to the chord line, and possessing all the other characteristics recited in claim 15. Like the appellant, we think that this claim language adequately provides notice as to the metes and bounds of claimed protection. Ex parte Rodgers, 27 USPQ 2d 1738, 1742-43 (B.P.A.I. 1992).

On examination of the claims, we are convinced that the examiner's holding of indefiniteness as to claim 1 is merely a matter of scope of the claim. This applies to the expression, guides associated with the sides of the diaphragm. This is not believed to be indefinite but merely broad. We find the elements set forth in terms which we regard as clear in meaning but admittedly of relatively broad scope. Since no prior art is relied upon, it is presumed that this scope of claim is and should be allowed as a patentable improvement over the state of the art. Ex parte Hendrickson, 42 USPQ 634, 635 (Pat. Off. Bd. App. 1939).

Accordingly, the Examiner's rejection of claims 41-46 under 35 U.S.C. Section 112, second paragraph, should be withdrawn.

**Rejection of Claims 41-46 under 35 U.S.C. Section 112, Second Paragraph**

The Examiner has rejected claims 41-46 under 35 U.S.C. Section 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps; steps by which the binding affinity would be determined and whereby HMGI biological activity is measured and quantified. The Examiner argues that the method of claims 41-43 merely determine binding affinity of a candidate compound, which is an unspecified physical measurement, but does not quantify any level of biological activity and the method of Claims 44-46 merely determines levels of reporter gene expression, which

indirectly determines the effect of a compound on a promoter. Applicants' claims as amended obviate the Examiner's rejections.

As set out above, applicants have cancelled claims 41-44 and have merged the subject matter of claim 41 and claim 44 into new claim 47. Applicants method of determining the binding affinity of a candidate compound as set out in claim 47 recites as follows:

> A method for screening candidate compounds capable of inhibiting HMGI biological activity which comprises the steps of :
>
> (a) immobilizing an HMGI protein, or a fragment thereof, on a solid surface;
>
> (b) incubating the HMGI protein, or a fragment thereof, with a candidate compound under conditions which promote optimal interaction; and
>
> (c) identifying candidate compounds which bind to the HMGI protein, or a fragment thereof; and
>
> (d) measuring the binding affinity of the candidate compounds in step (c);
>
> (e) transfecting into a cell a DNA construct which contains a reporter gene under the control of an HMGI protein-regulated promoter;
>
> (f) administering to the cell a candidate compound from step (c);
>
> (g) measuring the levels of reporter gene expression in the presence and absence of the candidate compound; and
>
> (h) determining from the levels of reporter gene expression which candidate compounds modulate the HMGI biological activity.

Accordingly, the Examiner's rejection of claims 41-46 under 35 U.S.C. Section 112, second paragraph, should be withdrawn.

**Rejection of Claims 41-43 under 35 U.S.C. 112, First Paragraph.**

The Examiner has rejected claims 41-43 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that the factors most relevant to this rejection are the amount of direction or guidance presented and the amount of experimentation necessary. The Examiner notes that the claims are drawn to a method for screening candidate compounds capable of inhibiting HMGI biological activity, and that the method, in one embodiment, is accomplished using a fragment of a HMGI protein and, in all embodiments, is accomplished by determining a binding affinity for the candidate compound. First, the Examiner states that the "fragment thereof" can be broadly interpreted to mean a single amino acid and as such would not accomplish the claimed method since a single amino acid would not be related to HMGI function. Second, the Examiner states that determination of a binding affinity, by unspecified means, does not determine which candidate compounds inhibit HMGI biological activity. Third, the Examiner states that the claimed method does not teach how a reduction in biological activity would be quantified to meet the limitations of claims 42 and 43. The Examiner argues that since it is not routine in the art to engage in de novo experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to practice the claimed method. Without such guidance, the Examiner argues that the experimentation left to those skilled in the art is undue. Applicants traverse the Examiner's rejections.

Fragments are well know in the art. A fragment is a polypeptide having an amino acid sequence that entirely is the same as part, but not all, of the

amino acid sequence of the aforementioned HMGI polypeptides. Preferred fragments include, for example, truncated polypeptides having the amino acid sequence of HMGI polypeptides, except for deletion of a continuous series of residues that includes the amino terminus, or a continuous series of residues that includes the carboxyl terminus, or deletion of two continuous series of residues, one including the amino terminus and one including the carboxyl terminus. Also preferred are fragments characterized by structural or functional attributes such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding regions, DNA binding regions, and high antigenic index regions. Other preferred fragments are biologically active fragments. Biologically active fragments are those that mediate HMGI activity, including those with a similar activity or and improved activity, or with a decreased undesirable activity. Also included are those that are antigenic or immunogenic in an animal, especially in a human.

It has been consistently held that the first paragraph of 35 U.S.C. Section 112 required nothing more than objective enablement.... In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well-known in the art.... How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. Section 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support... The error we see in Staehelin's approach to the question before us is that Staehelin

would require a patent specification to be a blueprint which, if followed, would unfailingly reproduce exactly an applicant's claimed invention. However, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC Section 112, first paragraph. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (B.P.A.I 1992).

In order to be entitled to the benefit thereof, it is not necessary that a patent application exactly describe the limitations of a claimed process, but only so clearly that those skilled in the art would recognize from the disclosure that applicant invented the claimed process, including those limitations. *In re Wertheim et al.*, (C.C.P.A. 1976) 541 F2d 257, 191 U.S.P.Q. 90.

Accordingly, the Examiner's rejection of claims 41-43 under 35 U.S.C. 112, first paragraph, should be withdrawn.

**Rejection of Claims 44-46 under 35 U.S.C. Section 112, First Paragraph.**

The Examiner has rejected claims 44-46 under 35 U.S.C. Section 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that the factors most relevant to this rejection are the amount of direction or guidance presented and the amount of experimentation necessary. The Examiner notes that the claims are drawn to a method for screening candidate compounds capable of inhibiting HMGI biological activity. The Examiner states that the method is accomplished using a host cell comprising a reporter gene under control of an HMGI protein-regulated promoter in the presence of a candidate compound. First, the Examiner states that the specification does not teach any

HMGI protein-regulated promoter and therefore the skilled artisan would not know with what material to begin the assay. Second, the Examiner states that the determination of a reporter gene expression, by unspecified means, does not determine which candidate compounds inhibit HMGI biological activity. Third, the Examiner states that the claimed method does not teach how a reduction in biological activity would be quantified to meet the limitations of claims 45 and 46. The Examiner argues that since it is not routine in the art to engage in de novo experimentation where the expectation of success is unpredictable, the skilled artisan would require additional guidance in order to practice the claimed method. Without such guidance, the Examiner argues that the experimentation left to those skilled in the art is undue. Applicants traverse the Examiner's rejections.

Applicants recite in the specification at page 54, lines 31-35:

> In this assay, a DNA construct containing a reporter gene such as luciferase gene under control of a HMGI-regulated promoter such as human interferon-ß promoter (Thanos and Maniatis, 1992) is transfected into a cell line which expresses proteins required for induction of human interferon-ß gene, i.e., NF-kb, ATF-2 and an HMGI genes.

Thus, an example of an HMGI protein-regulated promoter would be the human interferon-beta promoter. As set out above, the biological activity of HMGI proteins is to regulate transcription. Thus, levels of activity of a reporter gene, such as luciferase, under the control of an HMGI regulated promoter, such as the human interferon-beta promoter, indicate levels of HMGI biological activity. What would be measured are changes of the level of transcription or expression of a reporter gene under the control of an hMGI protein-regulated promoter in the presence of a compound which binds HMGI-C, relative to the absence of such a

compound, indicating that the compound modulates the activity of the HMGI proteins.

Accordingly, the Examiner's rejection of claims 44-46 under 35 U.S.C. Section 112, first paragraph, should be withdrawn.

**Rejection of Claims 44-46 under 35 U.S.C. 112, First Paragraph.**

The Examiner has rejected claims 44-46 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner states that the claimed method recites a step whereby a cell is transfected with "a DNA construct which contains a reporter gene under control of an HMGI protein-regulated promoter". The Examiner argues that the specification does not disclose any HMGI protein-regulated promoter and that a description of the DNA is required to adequately describe the claimed invention. Accordingly, the Examiner concludes that an adequate written description of a DNA requires more than a mere statement that it is a part of the invention and reference to a potential method for isolating it, what is required is a description of the DNA itself. Given this lack of adequate written description, the Examiner argues that applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would not recognize applicants were in possession of the claimed invention. Applicants traverse the Examiner's rejection.

As set out above, applicants recite in the specification at page 54, lines 31-35: "In this assay, a DNA construct containing a reporter gene such as

luciferase gene under control of a HMGI-regulated promoter such as human interferon-ß promoter (Thanos and Maniatis, 1992) is transfected into a cell line which expresses proteins required for induction of human interferon-ß gene, i.e., NF-kb, ATF-2 and an HMGI genes." Thus, an example of an HMGI protein-regulated promoter would be the human interferon-beta promoter. As set out above, the biological activity of HMGI proteins is to regulate transcription. Thus, levels of activity of a reporter gene, such as luciferase, under the control of an HMGI regulated promoter, such as the human interferon-beta promoter, indicate levels of HMGI biological activity. What would be measured are changes of the level of transcription or expression of a reporter gene under the control of an hMGI protein-reguated promoter in the presence of a compound which binds HMGI-C, relative to the absence of such a compound, indicating that the compound modulates the activity of the HMGI proteins.

Accordingly, the Examiner's rejection of claims 44-46 under 35 U.S.C. 112, first paragraph, should be withdrawn.

Aberrations in the genetic mechanisms that control growth and proliferation have emerged as a primary event in carcinogenesis. The function of HMGI-C and HMGI(Y), two embryonically e HMGI-C and HMGI(Y), two emb investigated because their expression is highly associated with tumor development. Disruptions of either HMGI-C or HMGI(Y) in humans result in a diverse array of solid mesenchymal tumors. Most prominent among these neoplasms are uterine leiomyomata, the most common pelvic tumors in women and the indication for over 200,000 hysterectomies annually in the United States. In tumors of mammary and thyroid glands as well as in prostate cancer, HMGI expression is highly correlated

with tumor progression and metastasis, suggesting that these proteins can be used for as progression markers for a variety of tumor types.

Further proof for the pivotal role of HMGI proteins in both normal and pathological growth was obtained in the mouse system. Homologous recombination was used to inactivate murine HMGI-C gene. Demonstrating the importance of the HMGI genes in growth regulation, HMGI-C knockout mice exhibit significant growth retardation (mutant mice are 60% smaller than their wild-type littermates) with the reduction in most tissues commensurate with the overall decrease in the body weight. Even more importantly, these pygmy mice are highly resistant to chemically induced skin cancer. Specifically, the frequency of tumor development in the knockout mice is 40% of that in the control animals and tumor multiplicity exhibits a 20-fold decrease. Independently, inhibition of HMGI-C synthesis was shown to render thyroid epithelial cells intransigent to retroviral transformation. At the molecular level, HMGI proteins function in transcriptional regulation by promoting cooperative binding of the transcription factors to DNA. Deregulation of the downstream target genes can easily account for the important biological roles of the HMGI proteins as well as for the dramatic consequences of their inappropriate expression.

Lipomas are one of the most common mesenchymal neoplasms in humans. They are characterized by consistent cytogenetic aberrations involving chromosome 12 in bands q14-15. Interestingly, this region is also the site of rearrangement for other mesenchymally derived tumors. The present invention demonstrates that HMGI-C, an architectural factor that functions in transcriptional regulation, has been disrupted by rearrangement at the 12q14-15 chromosomal breakpoint in lipomas. Chimeric transcripts were isolated from two lipomas in which HMGI-C DNA-binding domains (A-T hook motifs) are fused to either a LIM

or an acidic transactivation domain. These results identify the first gene rearranged in a benign neoplastic process that does not proceed to a malignancy and suggest a role for HMGI-C in adipogenesis and mesenchyme differentiation.

HMGI-C is an attractive candidate gene to be implicated in lipoma formation. This gene is required in transformation and is a transcriptional regulatory factor as are many genes identified at translocation breakpoints in a variety of tumors. Secondly, disruption of HMGI-C leads to mice of small stature which, most intriguingly, have disproportionately less body fat than normal littermates. Finally, mouse HMGI-C maps to a region syntenic to human 12q14-15 which is the area most frequently rearranged in lipomas. Therefore, the human homolog of the mouse HMGI-C gene was cloned and its possible role in lipomas investigated.

Growth is one of the fundamental aspects in the development of an organism. Classical genetic studies have isolated four viable, spontaneous mouse mutants disrupted in growth, leading to dwarfism. Pygmy is unique among these mutants because its phenotype cannot be explained by aberrations in the growth hormone-insulin-like growth factor endocrine pathway. The present invention shows that the pygmy phenotype arises from the inactivation of HMGI-C and are critical in the assembly of stereospecific transcriptional complexes (Tjian & Maniatis, 1994). In addition, HMGI-C and the other HMGI family member, HMGI(Y)( Johnson et al., 1988), were found to be expressed predominantly during embryogenesis. The HMGI family are known to be regulated by cell cycle dependent phosphorylation which alters their DNA binding affinity (Reeves et al., 1991). Overall, these results demonstrate the important role of HMGI proteins in mammalian growth and development.

Among the most prominent characteristics consistently exhibited by cancer cells are karyotypic aberrations which disturb genes essential for the regulation of fundamental cellular processes. A wide array of solid mesenchymal tumors is characterized by recurrent rearrangements of chromosomal bands 12q13-15 or 6p21-23. This study shows that HMGI expression is normally restricted to undifferentiated, rapidly dividing cells but is activated in differentiated adipocytes following translocations of 12q13-15 or 6p21-23 in human lipomas. The present invention shows that the molecular pathway of tumor development is dictated by the precise nature of HMGI disruption and that HMGI misexpression in a differentiated cell is a pivotal event in benign tumorigenesis.

Uterine leiomyomata are the most common pelvic tumors in women and are the indication for more than 200,000 hysterectomies annually in the United States. Rearrangement of chromosome 12 in bands q14-q15 is characteristic of uterine leiomyomata and other benign mesenchymal tumors, and a YAC spanning chromosome 12 translocation breakpoints was identified in a uterine leiomyoma, pulmonary chondroid hamartoma, and lipoma. Recently, it was demonstrated that HMGI-C, an architectural factor mapping within the YAC, is disrupted in lipomas, resulting in novel fusion transcripts. This study concerns the localization of translocation breakpoints in seven uterine leiomyomata 10 to $>100$ kb upstream of HMGI-C by use of fluorescence in situ hybridization. These findings suggest a different pathobiologic mechanism in uterine leiomyomata from that in lipomas. HMGI-C is the first gene identified in chromosomal rearrangements in uterine leiomyomata and has important implications for an understanding of benign mesenchymal proliferation and differentiation.

Recently, molecular dissection of this chromosomal region has substantiated this hypothesis. To identify a gene at the breakpoint on chromosome

12 in uterine leiomyomata, a high-density physical map of the t(12;14) breakpoint region was constructed and identified a YAC, 981f11, that spans the translocation breakpoints in a uterine leiomyomata, pulmonary chondroid hamartoma and a lipoma. Further detailed characterization showed that the gene for HMGI-C, an architectural factor that is a non-histone component of chromatin, maps within 981f11 and is disrupted in lipomas. HMGI-C is rearranged in lipomas with chromosome 12 translocations, resulting in novel chimeric transcripts that fuse the DNA-binding A-T hook domains of HMGIC with potential transcriptional activation domains.

In view of the foregoing Amendment and Response, applicant requests reconsideration pursuant to 37 C.F.R. Section 112 and allowance of the claims pending in this application. Applicant requests the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference.

Applicant's attorney authorizes the Examiner to charge Deposit Account 13-4822 if there are any additional fees due in connection with this Amendment and Response.

Respectfully submitted,
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